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Incidence of type 2 diabetes in people with a history of hospitalisation for major mental illness in Scotland 2001-2015: a retrospective cohort study

Running title: Major mental illness and type 2 diabetes risk

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ABSTRACT

Objective To determine the incidence of type 2 diabetes in people with a history of hospitalisation for major mental illness versus no mental illness in Scotland, by time period and sociodemographics.

Research design and methods We used national Scottish population-based records to create cohorts with a hospital record of schizophrenia, bipolar disorder or depression, or no mental illness and to ascertain diabetes incidence. We used quasi-Poisson regression models including age, sex, time period and area-based deprivation to estimate incidence and relative risks (RRs) of diabetes by mental illness status. Estimates are illustrated for people aged 60 years and in the middle deprivation quintile in 2015.

Results We identified 254,136 diabetes cases during 2001-2015. Diabetes incidence in 2015 was 1.5 to 2.5-fold higher in people with versus without a major mental disorder, with the gap having slightly increased over time. RRs of diabetes incidence were greater among women than men for schizophrenia (RR 2.40 [95% CI 2.01, 2.85] and 1.63 [1.38, 1.94]), respectively) and depression (RR 2.10 [1.86, 2.36] and 1.62 [1.43, 1.82]), but similar for bipolar disorder (RR 1.65 [1.35, 2.02] and 1.50 [1.22, 1.84]). Absolute and relative differences in diabetes incidence associated with mental illness increased with increasing deprivation.

Conclusions: Disparities in diabetes incidence between people with and without major mental illness appear to be widening. Major mental illness has a greater effect on diabetes risk in women and people living in more deprived areas, which has implications for intervention strategies to reduce diabetes risk in this vulnerable population.

INTRODUCTION

The life expectancy of people with major mental illness, including schizophrenia, bipolar disorder or major depressive disorder, is reduced by 10-20 years compared to the general population (1-3). This excess mortality is largely due to an increased risk of cardiovascular disease (3-6), for which type 2 diabetes mellitus is a major risk factor. Numerous studies have reported the higher prevalence of diabetes among those with a major mental disorder. Recent meta-analyses have demonstrated that, although estimates vary substantially across studies, the prevalence of type 2 diabetes is about 10% in those with schizophrenia and bipolar disorder and about 8% in those with major depressive disorder (7-10). This relates to about a two-fold increased prevalence of diabetes when compared to the general population after adjusting for age, and could extend to as much as a three- to four-fold excess risk in some sub-groups of the population. However, these estimates are almost entirely derived from cross-sectional studies, with few existing prospective studies on the incidence of diabetes in those with major mental illness. Where prospective studies have been carried out, these have focused far more on diabetes incidence among people with depression (11-13) than schizophrenia or bipolar disorder (14, 15).

The association between major mental illness and diabetes is explained at least in part by key lifestyle factors such as body mass index which are known to be associated with mental illness and are also major risk factors for type 2 diabetes.

The relationship between major mental illness and diabetes risk factors might vary with age, sex and socioeconomic status, providing the rationale for examining whether the association between major mental illness and subsequent diabetes might differ by sociodemographic factors. We know remarkably little about how the association between major mental disorder and diabetes incidence differs by these

sociodemographic factors. Meta-analyses have suggested that the association between depression in general and type 2 diabetes may be more marked in younger than older people (11), but this is derived from cross-study comparisons rather than investigation of age differences within the same study population. Also, the prevalence of co-morbid mental disorder and diabetes prevalence has been proposed to be higher in women than men (8, 16), again based on cross-sectional data, with few prospective studies reporting sex-specific associations of co-morbid mental disorder and diabetes. To our knowledge no study has prospectively examined how the association between mental illness and type 2 diabetes differs by socioeconomic status. Similarly, to our knowledge, there have been no studies of time trends in type 2 diabetes incidence by major mental illness status and so it is also unclear whether the difference in risk has narrowed or widened over time. Therefore, in the present study we examined incidence of type 2 diabetes in Scotland from 2001-2015 among those with a prior hospital record for major mental illness versus those without a history of hospitalisation for any mental health disorder, exploring differences by time period, age, sex and socioeconomic status.

METHODS

We used the dataset of the General Acute inpatient and Day Case - Scottish Morbidity Records (SMR01) and the Mental Health Inpatient and Day Case dataset (SMR04) to identify hospital admissions where the discharge diagnoses included schizophrenia (International Statistical Classification of Diseases [ICD] 10 F20 and F25 and ICD9 295.0 to 295.3, 295.6 to 295.9), bipolar disorder (ICD10 F30 to F31 and ICD9 296.0 to 296.1, 296.4 to 296.7) or depression (ICD10 F32-F34 and ICD9 296.2 to 296.3, 298.0, 311). We applied a hierarchy of severity to assign people to one group only, ranking disorders as schizophrenia, bipolar disorder and depression;

thus, someone with a record of both bipolar disorder and depression was assigned to the bipolar group only. Individuals entered the cohort from the date of first hospital admission for the most severe of the three disorders. We identified prevalent cases of mental health disorder among those aged 18 years or older between 1st January 1981 and 31st December 2014. We initially carried out [exploratory analyses to investigate whether associations differed for people with an uncomplicated mental illness \(i.e. diagnosis of a single mental illness\) and complex mental illness \(i.e. diagnoses of multiple mental illnesses\)](#). The patterns of associations were broadly similar and so we did not stratify data in the final analyses.

Comparison cohort

Our comparison cohort was derived from the total general population, after removing people who had a hospital record for any mental illness listed in ICD10 chapter 5 (mental and behavioural disorders) or the corresponding ICD9 codes, with the exception of organic disorders (F00-F09) and mental retardation (F70-F79). Details of the ICD codes used are provided in Supplementary Table S1.

Type 2 diabetes

We identified incident cases of type 2 diabetes through a research extract of the Scottish Care Information – Diabetes (SCI-Diabetes) dataset. This national diabetes register includes approximately 99% of all patients diagnosed with diabetes since 2004 (17), collating information from primary and secondary care clinics on clinical care, demographic and lifestyle factors. It also includes information on people diagnosed with diabetes between 2001 and 2004 and who did not die during that time period. For research purposes, an algorithm is used to differentiate between type 1 and type 2 diabetes, based on clinician-recorded diagnosis, prescription data and age at diabetes diagnosis. In this study, we included all incident type 2 diabetes

cases occurring between 1st January 2001 and 31st December 2015

Person-time

We calculated person-time (in fractional years) for the mental health cohort from the date of hospital admission with a mental health disorder until the end date of follow up. We followed the cohort until the earliest of type 2 diabetes diagnosis date, date of death, or end of follow-up (31st December 2015). We obtained person-time for the comparison population via mid-year estimates of the population. Person-time after an event was subtracted from the estimates in each year.

Events and person-time were broken down by calendar year, age in 5-years categories, sex and area-based deprivation. The latter was defined using quintiles of the Carstairs Index, which uses census data at postcode level on lack of car ownership, low occupational social class, overcrowded households and male unemployment to create a measure of material deprivation of an area (18).

Statistical analyses

We summarised baseline characteristics for the complete cohort and calculated age-standardised type 2 diabetes incidence rates, per 1000 person-years (pyrs), using the 2013 European Standard Population (see <http://www.isdscotland.org/Products-and-Services/GPD-Support/Population/Standard-Populations/> for more details). We fitted quasi-Poisson models with incidence of type 2 diabetes as the outcome, which included main effects for history of a mental illness, age, sex, time period and area-based deprivation index and all two-way interactions. Age (using the mid-point of each 5-year block) and time period were modelled as continuous variables using natural cubic splines. Area-based deprivation index was modelled as a categorical variable. The models were used to calculate relative risks (RRs). All analyses were conducted using R software (19).

Ethics approval

Approval for the linkage of the administrative health datasets used in this study was provided by the NHS Scotland Public Benefit and Privacy Panel for Health and Social Care. Approval for the use of diabetes data was obtained from the Scottish Diabetes Research Network and ethics approval was obtained from the South East Scotland Research Ethics Committee (reference 16/SS/0152).

This article is written in accordance with the Strengthening Reporting of Observational Studies in Epidemiology (STROBE) (20) and Reporting of Studies Conducted using Observational Routinely-collected health data (RECORD) (21) statements.

RESULTS

Between 2001 and 2015 there were 246,046 incident type 2 diabetes mellitus cases in Scotland among people with no prior hospital record of a mental illness and 2315 among those with a hospital record for schizophrenia, 1720 among those with bipolar disorder and 4055 among those with depression.

Type 2 diabetes incidence by mental health status, age and sex

Type 2 diabetes incidence increased with increasing age (until about 60 years) in all groups, but tended to peak at an earlier age among people with a mental disorder compared to those with no history of mental illness. Thus, the average age of type 2 diabetes onset was lower in people with an admission for schizophrenia (mean 51.4 years \pm 12.6 SD) and depression (mean 57.6 \pm 13.1 SD), but not bipolar disorder (mean 60.0 \pm 12.1 SD) compared to the population with no mental illness (mean 60.8 \pm 13.2 SD; Supplementary Table S2). In all comparison groups, age of onset was slightly younger in men than women and in the most versus least deprived in all

groups. The age-standardised incidence of type 2 diabetes at all time points was higher among people with a hospital record for each mental disorder than the group without mental illness (Supplementary Table S3). This concurred with predicted incidence rates obtained from quasi-Poisson models, as illustrated in Figure 1, which shows type 2 diabetes incidence by age for the middle deprivation quintile, in 2001 and 2015. Absolute rates of type 2 diabetes were higher in men than women in all cohorts, although the difference in incidence was smaller for people with schizophrenia and bipolar disorder (Figure 1).

Time-trends in diabetes incidence by mental disorder

Between 2001 and 2015, age-standardised type 2 diabetes incidence decreased overall in the group with no history of mental illness, in both men and women. Among those with schizophrenia and bipolar disorder, type 2 diabetes incidence increased between 2001 and 2008 and then started to decrease up to 2015. In contrast, incidence of type 2 diabetes increased between 2001 and 2015 among people with a hospital record for depression. These findings are illustrated in Figure 2 using data from men and women aged 60 years and in the middle deprivation quintile. We observed similar patterns of type 2 diabetes incidence among those aged 40 and 50 years (especially for depression), although there was less of a decline in incidence in the cohort without mental illness compared to the 60 year-olds and diabetes incidence tended to plateau from 2008 onwards in people with schizophrenia and bipolar disorder (supplementary Figure 1). In general, having a hospital record for each mental disorder was associated with increased incidence of type 2 diabetes when compared to the group without mental illness. For example, in 2015, among men aged 60 years and in the middle deprivation quintile, type 2 diabetes incidence was higher in those with schizophrenia (RR 1.63, 95% CI 1.38 to 1.94), in men with

bipolar disorder (RR 1.50, 95% CI 1.22 to 1.84) and in men with depression (RR 1.62, 95% CI 1.43 to 1.82), compared to the group with no mental illness (Figure 2 and Supplementary Table S4). RRs were greater among women than men, with incidence of type 2 diabetes in 2015 almost two-and-a-half-fold higher in women with schizophrenia (RR 2.40, 95% CI 2.01 to 2.85), 65% higher in those with bipolar disorder (RR 1.65, 95% CI 1.35, to 2.02) and two-fold higher in those with depression (RR 2.10, 95% CI 1.86 to 2.36) compared to the group with no mental illness (Figure 2 and Supplementary Table S4). Among both men and women, RRs compared to the group without mental illness among those aged 60 years increased over time for the schizophrenia, depression and, to a lesser extent, bipolar disorder cohorts, (Figure 3 and Supplementary Table S4). RR estimates over time followed similar patterns at ages 40 and 50 years (Supplementary Figure 2).

Type 2 diabetes incidence by mental disorder, sex and deprivation level

The proportion of people in the most deprived quintile was much higher in the cohorts with schizophrenia (32.8%), bipolar disorder (27.0%) and depression (27.0%) than the comparison group (21.7%; Supplementary Table 2). Type 2 diabetes incidence was positively associated with deprivation among women in all cohorts and men with a mental disorder, as illustrated in Figure 4. We did not observe a deprivation gradient in type 2 diabetes incidence among men without mental illness at 60 years of age, but did at age 40 years (supplementary Figure 3). For all disorders, the RR of type 2 diabetes incidence was greatest among people in the most deprived quintiles (Supplementary Table S5). For instance, in 2015 the RR for type 2 diabetes incidence in 60 year-old men with versus without schizophrenia in the most deprived quintile was 1.69 (95% CI 1.45 to 1.98) whereas in the association for men with versus without schizophrenia in the least deprived quintile was not

statistically significant (RR 1.09, 95% CI 0.88 to 1.36). A similar pattern was observed among men with bipolar disorder and depression. RRs for women were larger than men for all mental disorder groups. As with men, RRs were positively associated with deprivation, but in contrast to men, the association was statistically significant in the least deprived group. For example, schizophrenia was associated with a two-and-a-half-fold (RR 2.48, 95% CI 2.12 to 2.91) and a 60% (RR 1.60, 95% CI 1.28 to 2.01) increased risk of type 2 diabetes incidence in the most and least deprived quintiles, respectively (Supplementary Table S5). The larger relative risks in women than men are only partly due to lower absolute rates of diabetes in women than men, since we observed a greater difference in type 2 diabetes incidence among those with versus without schizophrenia (and to a lesser degree, depression) in women compared to men (Supplementary Figure 4). Therefore, having a hospital record for schizophrenia or depression is more strongly associated with incidence of type 2 diabetes in women than men in all deprivation groups, but particularly the most deprived groups.

CONCLUSIONS

Main findings

In Scotland, having a hospital admission for major mental illness is associated with a one-and-a-half to two-and-a-half-fold higher risk of type 2 diabetes incidence, with relative risk for those with compared to those without mental illness appearing to have increased over the last 15 years. In people with a hospital admission for schizophrenia or depression, type 2 diabetes incidence occurs at a younger age compared to people without a hospital admission for major mental illness. We found important sociodemographic differences, with the absolute and relative effects of mental illness being stronger in women than men and in deprived sub-groups,

indicating a greater impact of mental illness on type 2 diabetes risk in women and in people living in more deprived areas.

Strengths and limitations

To our knowledge, this is the first study to examine time trends in type 2 diabetes incidence by mental health disorder status, the first to examine differences in incidence by socioeconomic status and one of the first to investigate whether the prospective association differs by age and sex. Other strengths include the objective ascertainment of a diagnosis of type 2 diabetes, which was more than 99% complete from 2004 onwards, being based on a national diabetes register which collates information from primary care and secondary care clinics. The national scale and long-term running of the diabetes register also led to the inclusion of large numbers of diabetes cases, thus facilitating the investigation of interaction by time, age, sex and socioeconomic status.

Our study does however have some shortcomings. The main limitation is that, in the absence of national primary care data for research purposes, our definitions of major mental disorders were based on hospital records only. Therefore our findings may not be generalizable to those with a mental disorder who have never had their disorder recorded in hospital. This limitation is mitigated by the fact that hospital records extend as far back as 1981. Since we used both psychiatric and general hospital admission records to identify people with depression, there may have been selection bias in that people with less severe depression may have been included purely because they were admitted to a general hospital for an unrelated disease/episode. It is difficult to speculate how the definition of depression might have affected the results, since it could have both over-estimated the association between depression and diabetes (if a dose-response relationship exists between

depression and diabetes risk) or have under-estimated the association since people with depression that has not been recorded in hospital would not have been identified. Also, it is possible that those with a major mental disorder and admitted to hospital would be more likely to have their diabetes diagnosed, purely through having more contact with the health service. Also, we were not able to identify whether the associations differed depending on whether the mental illness diagnosis was recorded from psychiatric or acute hospital medical records; it would be of interest to explore this in future research. Finally, we were unable to adjust for factors known to be associated with mental illness and to be major risk factors for type 2 diabetes, such as use of psychotropic medications, sleep disruption, low physical activity and poor dietary choices that influence BMI, the key risk factor for type 2 diabetes. However, given that BMI may lie on the causal pathway between mental illness and type 2 diabetes, one could argue that minimally adjusted estimates more accurately convey the associated risk of diabetes.

Interpretation in context of previous studies

Despite the limitations of our study, our findings are consistent with previous prospective studies on the association between major mental disorders and type 2 diabetes incidence. In general, cohort studies have found that depression is associated with a 30-100% increased risk of type 2 diabetes prior to adjustment for lifestyle factors (11-13) and schizophrenia and bipolar disorder with a 70-80% increased risk of type 2 diabetes (14).

The slight decline in type 2 diabetes incidence observed among those with no hospital record for mental illness in our study is in line with overall trends in diabetes incidence in the general Scottish population (22). Since 2004, type 2 diabetes incidence in Scotland has declined or stabilised, depending on sex, age and

socioeconomic status, which is thought to be attributed to stabilising obesity prevalence and intensified diagnosis of type 2 diabetes leading to a smaller number and proportion of undiagnosed type 2 diabetes cases (22). However, our study demonstrates that this stabilisation or decline in type 2 diabetes incidence has not been observed among people with major mental illness. [The link between major mental illness and excess risk of type 2 diabetes in people with a major mental disorder are multi-factorial and complex. Contributing factors include environmental, genetic and lifestyle factors. Drug treatment may also play a role, with antipsychotic and anti-depressant medication having been linked to type 2 diabetes via weight gain and other metabolic abnormalities\(23, 24\). Furthermore, mental illness itself may have a direct physiological effect. For instance, there is growing evidence of glucose homeostasis disruption among anti-psychotic-naïve individuals presenting with first episode schizophrenia \(25\).](#) Many mechanisms ultimately increase risk of obesity, the key risk factor for type 2 diabetes. The apparent increase in diabetes incidence over time among those with a major mental illness in our study could be due to a number of factors, including improved diabetes diagnosis in this group over time. Primary care screening for cardiometabolic disease in general and among people with mental illness was incentivised through the Quality and Outcomes Framework, a pay-for-performance scheme for general practitioners, which was in place in Scotland between 2004 and April 2017 (26). This offered a financial reward to promote good practice against a set of evidence-based indicators, including monitoring of cardiometabolic risk in people with mental illness. The increase in type 2 diabetes incidence among those with a schizophrenia might also reflect the introduction, and more widespread use, of second generation antipsychotics, which, compared to first generation antipsychotics are thought to be associated with a

slightly higher increased risk of type 2 diabetes, via weight gain or effects on insulin resistance (27). However, it has been shown that all antipsychotics are associated with weight gain, albeit to varying degrees (28).

The observed sex differences in our study are interesting. A systematic review of studies found no sex difference in type 2 diabetes prevalence in people with and without bipolar disorder, which is in line with our findings on incidence (9). A later review by the same authors pooled together studies of patients with schizophrenia, bipolar disorder and major depression and found that prevalence of diabetes was about 40% higher in women than men (8), but since the analyses combined all mental disorders, it is unclear how sex differences might have differed by mental disorder. Consistent with our findings on depression, a recent prospective study reported greater effects of depression on type 2 diabetes risk in women than men (29). One explanation for our findings could be the higher prevalence of obesity in women with these mental health disorders compared to men and the larger relative gap in obesity between those with and without mental illness in women compared to men (30). It is intriguing that we did not observe similarly pronounced sex differences in the bipolar disorder group, given similar patterns of obesity by sex in this group. As with sex, previous studies have tended to adjust for socioeconomic status, rather than investigate potential interactions between mental disorders and socioeconomic status. Our findings indicate that, for all mental health disorders, the absolute and relative difference in diabetes rates are exacerbated by increasing level of deprivation, highlighting the additional vulnerability of people with a mental illness who live in deprived areas. Previous Scottish studies have found that the excess mortality associated with severe mental illness is most marked in the most deprived population groups (31), and that multimorbidity, including mental-physical health

comorbidity is more prevalent among more deprived groups (32). By demonstrating that the association between mental disorder and type 2 diabetes varies markedly by deprivation level, our study suggests that this increased diabetes risk is due largely to modifiable factors rather than intrinsic physiological effects of the mental illness itself.

Implications

The temporal and sociodemographic variations in the association between major mental disorders and diabetes have important implications for both clinical care and intervention strategies aimed at equitable improvement of physical health in people with mental illness. Sex and socioeconomic differences highlight the particularly high increased risk of type 2 diabetes among women and people living in more deprived areas with a mental illness. Reasons for these variations are likely multi-factorial and should be investigated further in future studies. Higher prevalence of obesity in women compared to men with mental illness could account for some of the observed sex differences in the association between mental illness and type 2 diabetes incidence. The importance of monitoring and attempting to improve the cardiometabolic health of people with major mental illness (and in particular, women and people with a low socioeconomic status) should continue to be emphasised to psychiatrists and primary care physicians. Novel intervention approaches aimed at reducing type 2 diabetes risk in people with mental illness should be tailored accordingly and involve targeted as well as universal strategies. Factors related to both socioeconomic status and mental illness, and amenable to intervention, include provision of care (33), health literacy (34), engagement with health services (35) and lifestyle behaviour. Whilst improvement of each of these is undoubtedly challenging, these must all be tackled if we are to reduce the risk of type 2 diabetes in people with

mental illness, particularly in more deprived areas. Furthermore, more pharmaco-epidemiological studies are urgently needed to improve our understanding of the potential adverse metabolic consequences of antipsychotics, mood stabilisers and anti-depressants. In an era of precision medicine, advances in the refined tailoring of psychotropic drug prescribing practices to optimise control of mental health symptoms and minimise side-effects on physical health may be possible in the future.

Conclusion

In Scotland, major mental illness is associated with a marked increased risk of incidence of type 2 diabetes, with evidence of increasing disparities in the last 15 years. The absolute and relative effects of mental illness are stronger in women than men and in more deprived sub-groups. These findings provide important insights into temporal and sociodemographic differences in type 2 diabetes risk across multiple mental health disorders, which have implications for clinical care and intervention strategies.

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CAJ, SHW, DJS, SWM and KL designed the study, JK and KF performed the analyses, all authors contributed to the interpretation of the results, CAJ drafted the manuscript which all authors commented on and approved for submission.

CAJ takes responsibility, as guarantor, for the study design, access to data and the decision to submit and publish the article.

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The authors declare no conflicts of interest.

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FIGURE LEGENDS

Figure 1 Type 2 diabetes incidence* among people in the middle deprivation quintile, for 2001 and 2015, by age, type or absence of mental disorder and sex

*Predicted incidence rates obtained from quasi-Poisson regression models including mental health status, age, sex, deprivation and time period, plus all mental health status and age interactions

Figure 2 Predicted type 2 diabetes incidence* among people aged 60 years and in the middle deprivation quintile by mental disorder, sex and year

*Predicted incidence rates obtained from quasi-Poisson regression models including mental health status, age, sex, deprivation and time period, plus all mental health status and age interactions

Figure 3 Relative risks of type 2 diabetes incidence among those with a hospital record for each mental disorder versus no mental illness, by sex, illustrated for people aged 60 years and in the middle deprivation quintile in 2015

Figure 4 Predicted diabetes incidence* by quintiles of area-based deprivation for each mental disorder, by sex, among people aged 60, in 2015

*Predicted incidence rates obtained from quasi-Poisson regression models including mental health status, age, sex, deprivation and time period, plus all mental health status and age interactions